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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,936	11/19/2001	Itamar Willner	WILLNER=5	4415

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EXAMINER	
YANG, NELSON C	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 10/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,936	WILLNER ET AL.	
	Examiner	Art Unit	
	Nelson Yang	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *79-140* is/are pending in the application.

4a) Of the above claim(s) *83-140* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *79-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/10/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group I, claims 79-82 in the reply filed on September 24, 2004 is acknowledged. The traversal is on the ground(s) that the prior art does not teach antibodies having the characteristics of the 5B3 monoclonal antibody as claimed. This is not found persuasive because antibody claimed in claim 79 includes antibodies comprising an altered antigen-binding portion where one or more of an amino acid residue has been added, deleted, or replaced by another amino acid residue, with the altered antigen-binding portion retaining substantially the same antigen-binding specificity as said antigen-binding portion. The claim does not recite what antigen the antigen-binding specificity is directed to, and therefore, this would include antigens that neither antibody has any specificity for. Since Rice teaches the presence of antibodies (column 4, lines 60-65), the antibody as claimed is taught.

2. The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 79-82 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 79 recites the limitation "an antigen-binding portion formed by two cooperating peptide sequences". It is unclear if this limitation is to be interpreted that the antigen-binding portion comprises the two peptide sequences, or if the two peptide sequences are somehow

involved in the construction of the antigen-binding portion. Furthermore, it is unclear how the peptide sequences are cooperating, whether, there are somehow physically linked, or if they are functionally linked.

6. Claim 79 refers to an altered antigen-binding portion. It is unclear if the alteration refers to the added, deleted, or replacement of one or more amino acid residues, or if it refers to something else, such as denaturation, changes in pH to the antigen binding portion, etc.

7. Claim 79 further recites that the altered protein has the same antigen-binding specificity as the unaltered protein. However, the claim fails to recite the antigen that the antigen-binding specificity refers to, and therefore, would include two proteins which have no antigen-binding specificity for the same antigens.

8. The term "substantially" in claims 79 and 82, is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear how would render two proteins to have "substantially the same antigen-binding specificity.

9. With respect to claim 80, it is unclear if applicant is claiming a protein that is "an antibody without the Fc region and a single chain antibody", or if those are separate embodiments of what the protein could be.

10. Claim 81 rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. This claim is an omnibus type claim. While applicant recites that the antibody is a monoclonal antibody designated herein as the 5B3 monoclonal antibody. It is unclear if the claim does in fact further limit claim 80, or if

it merely indicating that any monoclonal antibody of claim 80 is designated as a 5B3 monoclonal antibody.

11. With respect to claim 82, it is unclear if applicant is further claiming a second protein with substantially the same antigen binding specificity of the protein according to claim 81, or if applicant is referring to the same protein.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 79-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

14. The claims are broadly drawn to a protein comprising an "antigen-binding portion" that is in some way related in sequence to the sequences of 3A and 3B. As discussed under 35 U.S.C. 112, second paragraph, it is not clear which changes are encompassed or excluded by the scope of the instant claims; as such, the claim has been interpreted broadly to be drawn to any protein that binds to any antigen.

M.P.E.P. § 2163 recites, "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention...

one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to **immediately envisage** the product claimed from the disclosed process."

Applicant presents a limited working embodiment in which one monoclonal antibody, i.e. that having sequence identical to the sequences of 3A/3B, binds to two similar compounds, DNT and TNT. Applicant has not addressed the affinity of said antibody for any other antigen and has not provided any direction by which a given variant of said antigen might be identified as binding another antigen, or any guidance as to evaluating a given AA change when the antibody does not bind a given antigen. Similarly, applicants provide no guidance as to which AA changes might alter the kinetics of antigen binding, but not ameliorate binding altogether. Again, in claim 80, applicants claim a **fragment** of a protein having a given binding affinity, but no description is provided such that a person of ordinary skill in the art could immediately envisage which fragments would fulfill the requirements of the claims. One of ordinary skill simply could not immediately envisage which changes are encompassed by the instant claims and which are excluded.

Claim 80 further encompasses numerous nonexemplified embodiments for which no guidance is provided in the specification. The exemplified antibody is a mouse IgG1 antibody, but applicants provide insufficient disclosure to show possession, for example, of an IgM antibody. As the classes of immunoglobulins are distinct and have divergent properties, the specification fails to describe each and every embodiment recited in claim 80.

M.P.E.P. §2163 recites, "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus...when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. **For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.**"

The antibody binding and antibody specificity art is unpredictable; even a small sequence change can completely alter the specificity of a given antibody for a given substrate. Applicant has not provided an exhaustive list of relevant identifying characteristics of proteins having the claimed properties. Antigens that bind to proteins containing SEQ ID NOs 6 and 8, would not necessarily react with proteins that are less than 100% identical to SEQ ID NOs. 6 and 8. Colman [Colman, Effects of amino acid sequence changes on antibody-antigen interactions, 1994, Res Imm, 145, 33-36] and Lederman et al [Lederman et al, A single amino acid substitution in a common African allele of the CD4 molecule ablates binding of the monoclonal antibody, OKT4] teach that amino acid substitutions may abolish or significantly reduce antibody binding. Even a difference of a single amino acid could potentially necessitate the use of different, undisclosed antibodies. In short, identifying another protein with the claimed properties would require extensive experimentation for which no guidance has been provided.

The claims are currently in means-plus-function form, *i.e.* a protein binding an antigen with a given affinity. M.P.E.P. §2163 teaches that such claims are adequately described if "the written description adequately links or associates adequately described particular structure, material, or acts to the function recited in a means-plus-function claim limitation", or if "it is clear based on the facts of the application that one skilled in the art would have known what structure, material, or acts perform the function recited in a means-plus-function limitation". The instant disclosure does not meet either of these criteria. As detailed above, the specification does not link any specific compound to the claimed activity, and because of the diversity of the genus of proteins retaining binding affinity properties, the skilled artisan would not be able to determine which proteins do or do not perform the claimed function without extensive experimentation. See 35 U.S.C. §112, sixth paragraph.

15. Claim 79-82 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a polypeptide comprising Figs. 3A (SEQ ID NO: 6) and 3B (SEQ ID NO: 8), does not reasonably provide enablement for polypeptides that are less than 100% identical with the sequences of protein encoded by Figs. 3A (SEQ ID NO: 6) and 3B (SEQ ID NO: 8).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In particular, while a person of ordinary skill in the art would know to use proteins comprising the sequences of SEQ ID NO: 6 and 8, there are other polypeptide sequences that have not been disclosed which a person of ordinary skill in the art would not know what antibodies to use.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are broadly drawn to a protein formed by two cooperating peptide sequences, where the antigen-binding portion of at least one of the peptide sequences is of Fig. 3A and Fig. 3B except with an altered antigen binding portion in which one or more of an amino acid residue has been added, deleted or replaced by another amino acid residue. The specification, however, only discloses the polypeptides with SEQ ID NOs 6 and 8.

Applicant presents a limited working embodiment in which one monoclonal antibody, i.e. that having sequence identical to the sequences of 3A/3B, binds to two similar compounds, DNT and TNT. Applicant has not addressed the affinity of said antibody for any other antigen and has not provided any direction by which a given variant of said antigen might be identified as binding another antigen, or any guidance as to evaluating a given AA change when the antibody does not bind a given antigen. Similarly, applicants provide no guidance as to which AA changes might alter the kinetics of antigen binding, but not ameliorate binding altogether. Again, in claim 80, applicants claim a **fragment** of a protein having a given binding affinity, but no description is provided such that a person of ordinary skill in the art could immediately envisage which fragments would fulfill the requirements of the claims. One of ordinary skill simply could not immediately envisage which changes are encompassed by the instant claims and which are

excluded. As currently only SEQ ID NOs 6 and 8 have been disclosed, only polypeptides containing those sequences have been provided.

Furthermore, antigens that bind to proteins containing SEQ ID NOs 6 and 8, would not necessarily react with proteins that are less than 100% identical to SEQ ID NOs. 6 and 8. Colman [Colman, Effects of amino acid sequence changes on antibody-antigen interactions, 1994, Res Imm, 145, 33-36] and Lederman et al [Lederman et al, A single amino acid substitution in a common African allele of the CD4 molecule ablates binding of the monoclonal antibody, OKT4] teach amino acid substitutions may abolish or significantly reduce antibody binding. As can be seen, even a difference of a single amino acid could potentially necessitate the use of different, undisclosed antibodies. The fact that applicant have not recited the antigens to which the antigen-binding specificity refers further complicates the task of determining whether the antigen-binding specificity of the proteins has changed due to alteration of an amino acid.

The specification has provided insufficient direction or guidance and no working examples are provided to assist one skilled in the art to make and use the claimed proteins that are less than 100% identical to SEQ ID Nos 6 and 8. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

The claims encompass antibodies and antibody fragments which do not necessarily contain a full set of 6 CDRs and do not bind antigen or the same antigen as the parental non-human antibody and can retain a/some murine residue(s) in the framework regions (i.e., substantially identical to human framework regions). It is well established in the art that the

formation of an intact antigen-binding site of all antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, (textbook), 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al(Proc. Natl. Acad. Sci. USA 1982 Vol. 79: page 1979). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that humanized antibody, humanized scFv and fragments thereof as defined by the claims, which may contain less than the full complement of CDRs from the heavy and light chain variable regions have the required binding function. Applicants have provided insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing a humanized antibody, a humanized scFv and fragments thereof containing fewer than 6 CDRs, resulting in a humanized antibody that retains

the antigen specificity of the parental non-human antibody. One of skill in the art would neither expect nor predict the appropriate functioning of the antibody as broadly as is claimed.

Claim 80 encompasses numerous nonexemplified embodiments for which no guidance is provided in the specification. The exemplified antibody is a mouse IgG1 antibody, but applicants provide insufficient disclosure to show possession, for example, of an IgM antibody. As the classes of immunoglobulins are distinct and have divergent properties, the specification fails to describe each and every embodiment recited in claim 80.

In view of the lack of predictability of the art to which the invention pertains as evidenced by Coleman and Lederman et al and lack of guidance in the specification related to providing antibodies that specifically react with polypeptides encoded by polynucleotides with complements that hybridize to SEQ ID NO: 3, thereby forming an immunoconjugate which could be correlated with the presence or absence of Usher syndrome type IIa, undue experimentation would be required to practice the claimed method with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed invention and absent working examples providing evidence which is reasonably predictive that the claimed method is effective for polypeptides encoded by polynucleotides with complements capable of hybridizing to the polynucleotide sequence of SEQ ID NO: 3.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 79-82 rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Bastiaans [US 4,735,906].

With respect to claims 79-82, since the antibody claimed in claim 79 includes antibodies comprising an altered antigen-binding portion where one or more of an amino acid residue has been added, deleted, or replaced by another amino acid residue, with the altered antigen-binding portion retaining substantially the same antigen-binding specificity as said antigen-binding portion. The claim does not recite what antigen the antigen-binding specificity is directed to, and therefore, this would include antigens that neither antibody has any specificity for. Since Bastiians teaches the presence of monoclonal antibodies (column 8, example 6), the antibody as claimed is taught.

The limitation "designated herein as the 5B3 monoclonal antibody" in claim 81 has not been given any patentable weight as it seems to merely name the antibody, and does not appear to further limit the parent claim.

Conclusion

18. No claims are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nelson Yang whose telephone number is (571) 272-0826. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571)272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

20. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nelson Yang
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09/30/05